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Efficiency of Supplemental Vitamin D in Patients with Chronic Obstructive Pulmonary Disease

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Authors' contributions

Author BH designed the study, wrote the protocol and has major contribution in preparing manuscript. Author MM performed in clinical examination and treatment of patients, literature review, participating in preparing manuscript. Author MA clinical examination and treatment, study design, literature review, Participated in manuscript preparation. Author AF Performed laboratory tests, literature review, participated in writing method section. Author KHT study design, statistical analysis, participated in preparing manuscript. Author MM performed the data collection, literature review. All authors read and approved the manuscript.

Original Research Article

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ABSTRACT

Aims: To investigate the impact of supplemental vitamin D on pulmonary function in patients with stable chronic obstructive pulmonary disease (COPD).
Study Design: Case-control study
Place and Duration of Study: Department internal medicine, Rouhani hospital, Babol university of medical sciences, Babol, Iran. Over six months from September 2011 through February 2012
Methodology: Patients with COPD allocated to the treatment or control group intermittently. Thirty patients in the treatment group received 50.000 IU oral cholecalciferol

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weekly for two months plus routine treatment and 28 patients who served as controls received only their usual medications. The serum 25-hydroxyvitamin D (25-OHD) and FEV1% was measured at baseline and two months later. The primary objective was to determine treatment response defined as 5% or greater increase from baseline in FEV1% and the secondary objective was to determine the association between vitamin D supplementation and treatment response. In statistical analysis Spearman's correlation coefficient was used to determine correlation and logistic regression analysis with calculation of odds ratio (OR) was used to determine association.

Results: Mean age of the patients and controls was 67.1±10.5 years and 66.±12.2 years respectively (P=0.83).Thirteen patients (43.3%) versus 3 (10.7%) controls responded to treatment (*P*=0.009). Treatment response was positively correlated with mean serum 25-OHD changes from baseline (Spearman's correlation coefficient = 0.358, *P*=0.026). Mean 25-OHD change from baseline in the responders was significantly higher than in no responders (*P* = 0.031). Mean 25-OHD changes were positively correlated with FEV1% (*P* = 0.013).Vitamin D supplementation increased the treatment response by OR = 6.37 (95% CI, 1.57-25.8). After adjustment for inhaled bronchodilator, corticosteroid therapy, age, weight, smoking, ESR and CRP the odds of treatment response in vitamin D group increased to 17.1 (95%CI, 2.39-122, *P*= 0.005).

Conclusion: The findings of this study indicate that, two months vitamin D supplement to the drug regimen of COPD confers small pulmonary function improvement as compared with controls and justify serum 25-OHD measurement in COPD. Raising serum 25-OHD to sufficient levels with longer duration of treatment may exert further benefits.

Keywords: Vitamin D; chronic obstructive pulmonary disease; FEV1 improvement; may.

1. INTRODUCTION

Vitamin D deficiency is a worldwide problem affecting a substantial proportion of the general population over the world [1,2] .It is linked with the development as well as progression of several conditions including skeletal and non-skeletal diseases [1-5]. The impact of vitamin D deficiency has been addressed in several conditions like autoimmune diseases, chronic obstructive pulmonary disease (COPD) and cancer [3,6]. Patients with pulmonary diseases such as COPD, asthma, fibrocystic and interstitial lung diseases are at greater risk of vitamin D deficiency [7,8]. Vitamin D deficiency is more common in COPD and the prevalence of deficiency increases with the severity of disease stages [9-11] .Vitamin D deficiency seems to play a contributive role in the development of COPD exacerbation particularly during the winter season [12-15]. There is also a relationship between vitamin D and pulmonary function [16,17].

In COPD airflow inflammation occurs in responses to noxious particles and gases. These reactions are expected to be modulated by respiratory epithelial cells through converting inactive vitamin D to active form [10]. Active vitamin D plays important role in production of the antimicrobial peptide cathelicidin, inhibition of the dendritic cells activation, alteration of the T-cell activation and inhibition of chemokines production [15].

The potential of vitamin D in suppression of airway inflammation as well as in prevention of allergic asthma was shown in animal models [6,14]. Nevertheless, data regarding efficiency of vitamin D in patients with COPD are lacking. These observations provide a rational for vitamin D supplementation as an adjunct to the treatment of COPD. For these reasons the

present clinical trial was conducted to investigate the impact of supplemental vitamin D on pulmonary function in patients with stable COPD presented to an outpatient hospital clinic in Babol, Iran.

2. PATIENTS AND METHODS

2.1 Study Population

The study patients were derived from COPD patients presented the outpatient pulmonary clinic of Rouhani hospital, a university affiliated teaching hospital in Babol, north of Iran. Diagnosis of COPD was confirmed with compatible clinical features concurrent with airflow limitation defined as forced expiratory volume in 1 seconds (FEV1) to forced vital capacity (FVC) less than 0.70 (FEV1/FVC <70%) and FEV 1 < 80% predicted [18]. All patients had stable COPD without changes in FEV1% over three months prior to inclusion. Patients with COPD exacerbations were not included. The severity of COPD was assessed by Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [18]. Patients selection and treatment was performed over a six months period from September 2011 through February 2012. All patients were selected consecutively according to inclusion criteria among patients presented for follow up examination. All cases were males and eligible patients aged 40 years and older entered the study.

Exclusion criteria included, presence of pulmonary infection, tuberculosis, sarcoidosis, ILD, bronchiectasis, pleural effusion, congestive heart failure, primary pulmonary hypertension, pulmonary emboli, restrictive airway disease, conditions associated with altered vitamin D metabolism, absorption, patients with renal parenchymal diseases or renal stones, malignant disorders, taking medications containing vitamin D and oral corticosteroids. These conditions were excluded by appropriate methods like CAT, echocardiography, tuberculin skin test or other measures as clinically indicated

2.2 Data Collection

Data regarding age, previous illness, medications such as beta agonist and anticholinergic bronchodilators, inhaled corticosteroids, weight, smoking, opium addiction were collected by interview using a preprovided questionnaire. Serum vitamin D was assessed by quantitative determination of total 25-hydroxyvitamin D (25-OHD) using elecsys vitamin D total reagent according to the manufacturer's instruction [19]. The serum 25-OHD levels less than 20 ng/ml was considered as deficiency and 20-29.9 ng/ml as insufficiency and > 30 ng/ml as sufficient levels.

Additional data were provided to assess the inflammatory process by measuring serum C - reactive protein (CRP) and the ESR.

Serum CRP was measured by highly sensitive immunoturbidometric method using high sensitive kit provided by antibody against human CRP, and the ESR was determined by Westergren method.

2.3 Treatment

All patients received standard treatment by a single expert pulmonologist blinded to vitamin D supplementation. Patients were allocated to treatment or control group intermittently.

Treatment of COPD was performed accoding to guideline suggested by the GOLD [18]. The dosages of medications were modulated based on clinical judgment to achieve clinical improvement as far as possible.

Sample size estimation was based on detection of 20% intergroup difference in treatment response. A sample size of approximately 32 patients per group was needed to detect a significant difference at confidence level of 95% and power of 80%.

Oral vitamin D3 (Vit D3, Zahravi Co. Iran) was added to the therapeutic regimens of patients at dosage of 50.000 IU weekly for two months. The control group received only their routine medications without vitamin D3. All patients and controls were examined every 2-4 weeks as clinically indicated and followed over the study period. Post bronchodilator FEV1 volume, and FEV1%, serum 25-OHD level was assessed at baseline and at the end of the study period in all participants.

2.4 Statistical Analysis

The primary objective of this study was to determine and to compare frequency of treatment response rate in each group. Treatment response was defined as 5% or greater improvement in FEV1% from baseline at the end of the study period. The secodary objective was to determine the relationship between treatment response and vitamin D supplementation.

Normality of distribution for all continuous variables was examined by using measures of skewness and kurtosis as well as Kolmogrove-Smirnove test. Variables with normal distribution as assessed by the Kolmogorov–Smirnov test, were compared with parametric test and variables with skewed distribution were compared with Mann-Whitney U test. Spearman's correlation coefficient and logistic regression analysis with calculation of odds ratio (OR) and 95% confidence interval (95%CI) was used to determine association.

Ethical approval was granted from the research ethics Committee of the Babol University of Medical Sciences and the proposal of this study was registered in Iranian Registry of Clinical Trials as IRCT 20110315472482.

3. RESULTS

3.1 Patients Characteristics

A total of 65 male patients entered the study but 30 patients in the treatment group and 28 patients in the control group completed the study.

Mean age of patients and controls was 67.1±10.5 years and 66.5±12.2 years respectively (*P* =0.83).

Overall, 39 (78%) patients were smokers, 33 (56.9%) patients were using short acting inhaled bronchodilators such as salbutamol or ipatrupium, and 23 (39.7%) patients were using inhaled corticosteroid and all patients received long-acting beta agonists. In the entire study population, 40 patients (69%) were in stage 2 of GOLD; 17 (29.3%) patients were in stages 3 and 1 patient in stage 4 (Table 1). Overall 25 out of 57 patients (43.9%) had serum hs-CRP levels >3 mg/ L and 9 (15.5%) patients had ESR >15 mm/h.

Table 1. Comparison of baseline characteristics in the control and treatment groups of patients with chronic obstructive pulmonary disease treated with supplemental vitamin D

Patients characteristics		Control group N=28	Treatment group N=30	P
Age, years		65.5±12.2	67.1±10.5	0.83
Weight, Kg		62.8± 8.6	70±14.5	0.024
Serum 25-OHD ng/ml		28.7±6.1	27.5±11.4	0.61
ESR mm/h		6.9±7.6	10.3±9.7	0.14
Hs-CRP ® mg/ml		4±4.7	5.8±7.4	0.27
Smoking n(%)		16(69.6)	23(85.2)	0.16
Short acting β agonist bronchodilator n(%)		15(53.6)	18(60)	0.41
Inhaled corticosteroids n(%)		9(32)	14(46.7)	0.19
Staging	1	0	0	-
	2	22(78.6%)	18 (60%)	0.52
	3	6 (21.4%)	11(36.7%)	0.16
	4	0	1 (3.3%)	-

≠ Compared with t test ® serum high sensitive C-reactive protein

At baseline patients and controls were comparable according to FEV1%, serum 25-OHD, ESR, CRP and age. At the end of the study period 13 patients (43.3%) in the treatment group versus 3 (10.7%) controls responded to vitamin D treatment (*P* =0.009). There were no significant changes in medication dosages across the two study groups. No COPD exacerbations have occurred. In Table 2, Responders and non-responders were compared according to baseline values and serum 25-OHD changes from baseline. Mean serum 25-OHD change from baseline in responders was significantly higher than non-responders (6.26±12.2 ng/ml versus - 1.73±11ng/ml, *P* = 0.031)

Table 2. Comparison of responder and non-responder patients with chronic obstructive pulmonary disease according to baseline values and mean serum 25-hydroxyvitamin D (25-OHD) change from baseline after two months of supplemental vitamin D treatment

Variables	Nonresponders (n=42)	Responders (n =16)	P values β
Age, years	65.4±11.4	70.5±10.4	0.11
Weight, kg	65.8±12.4	68.6±12.8	0.46
Serum 25-OHD ng/ml	28.8± 9.3	26.2±8.7	0.32
FEV1%	57.6±13.5	51.8±13.5	0.32
ESR mm/h	7.5±8	11.8±10.4	0.14
Serum hs-CRP ® mg/ml	4.8±4.1	7.1±9.7	0.26
Mean serum 25-OHD change from baseline	-1.73±11	6.26±12.2	0.031

βCompared with t test ® serum high sensitive C-reactive protein

Changes from baseline in FEV1% was positively correlated to changes in serum 25-OHD (Spearman's correlation coefficient = 0. 324, *P*=0.013) (Fig. 1).

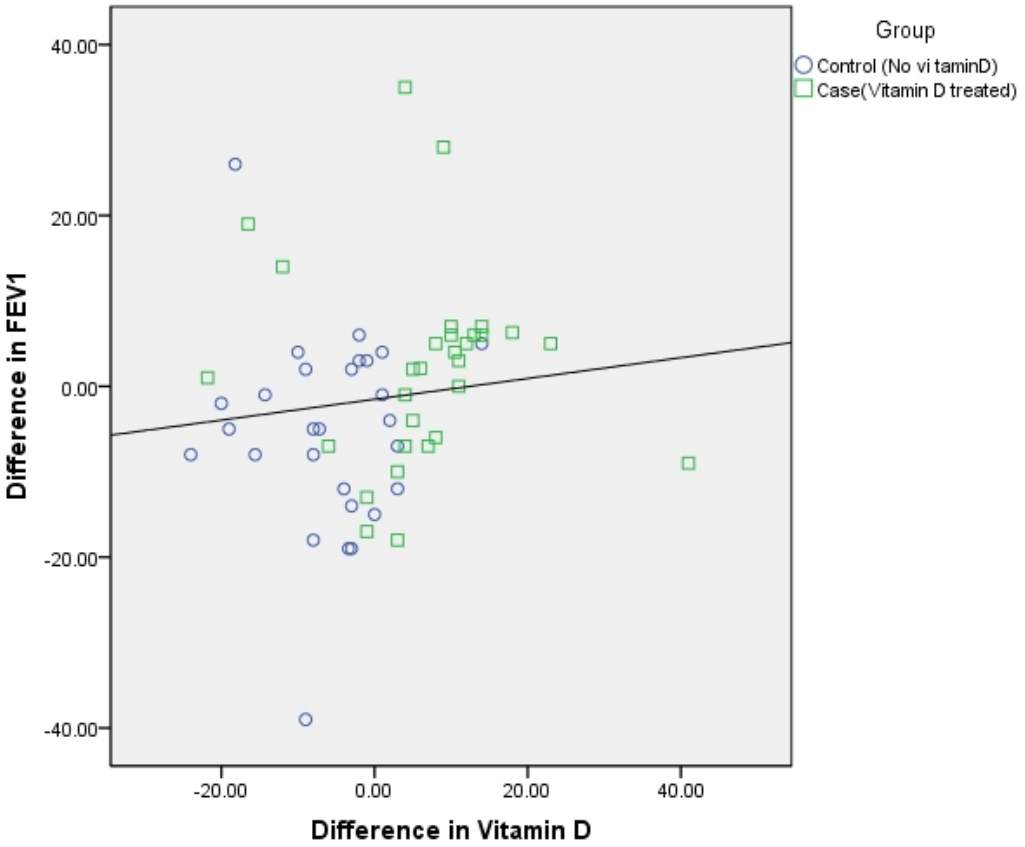

Fig. 1. Correlation between changes in serum 25-hydroxyvitamin D and FEV1% in patient as with chronic obstructive pulmonary disease treated with supplemental vitamin D for two months

There was also a significantly positive correlation between treatment response and mean serum 25-OHD change from baseline (Spearman's correlation coeficient = 0.387, *P* = 0.003). Vitamin D supplementation increased treatment response by OR = 6.37 (95% CI, 1.57-25.8). After adjustment for inhaled bronchodilator, corticosteroid therapy, age, weight, smoking, ESR, and CRP the odds of treatment response in the vitamin D treated group increased to 17.1 (95%CI, 2.39 -122, *P* = 0.005). Treatment response was positively correlated to ESR (Spearman's correlation coefficient = 0.317, P = 0.015). Median values of ESR in responders and non-responders were 8 mm/h (3-35 mm/h) and 4 (1.2-30) mm/h respectively (P = 0.017. Treatment response was not correlated to serum CRP, weight, baseline serum 25-OHD, or baseline FEV1% (Table 3).

Table 3. Relationship between vitamin D supplementation and treatment response ¥ in patients with chronic obstructive pulmonary disease (COPD) after adjustment for other potential confounders with calculation of odds ratio (OR) and corresponding 95% confidence interval (95%CI) and P values

Comparison groups	Coefficient (β)	SE (β)	OR(95%CI)	P values
Treatment vs controls	2.84	1.0	17.1(2.39-122)	0.005
ICS users vs nonusers	-1.7	1.02	0.18(0.025-1.35)	0.96
ISAB users vs nonusers	2.08	1.02	8.04(1.13-57.2)	0.037
Smokers vs nonsmokers	-0..19	1.08	0.82(0.09-6.8)	0.86
Age, years	0.039	0.037	1.04(0.96-1.11)	0.052

ICS=Inhaled corticosteroid ISAB=Inhaled short acting bronchodilators

¥ Treatment response defined as 5% or greater increase from baseline in percent predicted forced expiratory volume in 1 seconds (FEV1%) after treatment with supplemental vitamin D at 50.000 IU weekly for two months.

4. DISCUSSION

The results of this study indicated that supplementation of vitamin D to the drug regimen of COPD exerts small beneficial effect on pulmonary function in a subgroup of patients who had higher ESR and achieved higher levels of serum 25-OHD. Concordant raising of serum 25-OHD and FEV1% over the treatment period supports a contributive role for vitamin D therapy for improvement of pulmonary function. Significant positive correlation between changes in FEV1% and serum 25-OHD as well as logistic regression analysis provided additional documents in favor of independent association between vitamin D supplement and treatment response.

The results of this study are consistent with many earlier studies which addressed the relationship between vitamin D and FEV1 [12,16,17,20-24]. This study adds additional information to the existing literature in regard to beneficial effect of vitamin D in COPD.

Black et al, have shown a positive dose-response relationship between serum 25-OHD and FEV1 in patients of the Third National Health and Nutrition Examination Survey [16] Even in healthy subjects serum 25-OHD levels or daily intake of vitamin D was shown to be positively related with pulmonary function [22,24,25].

The benefit of vitamin D in the treatment of COPD has not been shown yet. Nevertheless, in one prospective double blind placebo controlled study of 182 patients with severe and moderate COPD, with history of recent exacerbations, Lehouck et al, administered 100.000 IU oral vitamin D or placebo every four weeks for one year to investigate the effect of high dose vitamin D in reducing the incidence of COPD exacerbations. In this study significant raising of serum 25-OHD concentrations in the treatment group, did not reduce exacerbation rates. Nevertheless, a subgroup of 30 patients with the initial severe serum 25-OHD deficiency (<10 ng m/l), benefitted from vitamin D treatment in terms of reducing exacerbation rate [12]. Inconsistent results may be attributed to inadequate sample size or short follow-up duration. Otherwise, with larger samples or longer follow-up period, detection of a significant difference would be possible. In another study, Konisaki et al, found no relationship between serum 25-OHD and risk of acute COPD exacerbations [13].

In the present study, a positive correlation between FEV1% and serum 25-OHD is compatible with the results of earlier studies which have shown a dose-response relationship between serum 25-OHD and FEV1 [16,17].

The beneficial effect of vitamin D on pulmonary airways has been attributed to anti-inflammatory effects of vitamin D [6,10,15]. Positive correlation between treatment response and ESR in the present study confirms this issue. However, lack of correlation between serum CRP and treatment response may be explained by inadequate sample size. Otherwise, CRP is a better marker of inflammation which is less affected by blood constituents such as fibrinogen and immunoglobulins, as well as the size, shape and number of red cells [26]. However, no laboratory markers have been recognized for evaluation of anti-inflammatory status in COPD.

The findings of this study should be considered with limitations. Duration of treatment was short, it is possible that longer duration of treatment would be associated with further raising of serum 25-OHD concentration and greater benefits, because, FEV1% improvement correlated with serum 25-OHD raising. In the present study efficacy of vitamin D was not compared with placebo group. Nonetheless, the observed improvement in FEV1% in this study should not be attributed to chance or biologic variations. Because, an independent association has been shown between treatment response and vitamin D supplementation by appropriate statistical method.

This study has strength in regard to positive correlation between treatment response and ESR indicating an inflammatory process in COPD responsive to vitamin D.

Another strength of this study is dependent to characteristics of the study population who were derived from a homogeneous population of COPD with similar lifestyle, sex and ethnicity. All patients presented to a single university affiliated clinic and treated similarly according to GOLD guideline [18]. Therefore, the possible confounders are expected to be distributed similarly across both treatment groups with minimal confounding effects.

5. CONCLUSION

This study indicates that vitamin D supplementation to the treatment regimen of COPD confers additional benefits in terms of pulmonary function improvement. Regarding to a positive relationship between serum 25-OHD and FEV1, these findings justify serum 25-OHD assessment in all patients with COPD and raising serum 25-OHD to sufficient levels.

The clinical significance of these findings in COPD patients requires further prospective studies with larger samples. Treatment with vitamin D should be continued for longer duration to achieve sufficient levels of serum 25-OHD.

It should be noted that the benefits of vitamin D supplementation in COPD is not limited to the lungs but extends beyond the pulmonary airways [27,28] and provides additional advantages over extrapulmonary organs such as muscles and bones.

CONSENT

Not applicable.

ETHICAL APPROVAL

Ethical approval was granted from the research Ethics Committee of the Babol University of medical sciences, Babol, Iran.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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